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An Observational Study of Bevacizumab-Induced Hypertension as a Clinical Biomarker of Antitumor Activity

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Key Words. Hypertension • Bevacizumab • Metastatic cancer • Dose intensity • Biomarker • VEGF

Disclosures: Olivier Mir: None; **Romain Coriat:** None; **Laure Cabanes:** None; **Stanislas Ropert:** None; **Bertrand Billemont:** None; **Jérôme Alexandre:** None; **Jean-Philippe Durand:** *Consultant/advisory role:* MSD-Chibret (Merck & Co Inc. France); **Jean-Marc Treluyer:** None; **Bertrand Knebelmann:** None; **François Goldwasser:** None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

Abstract

Background. **Hypertension is a common toxicity of bevacizumab, but the frequency of assessment of blood pressure and standardized grading remain to be defined. This study aimed to describe the incidence of bevacizumab-induced hypertension and factors associated with its development, then to retrospectively assess its relation with activity.**

Patients and methods. **One hundred nineteen patients with advanced or metastatic non-small cell lung cancer, colorectal cancer, or ovarian cancer receiving bevacizumab (2.5 mg/kg per week) and chemotherapy were eligible for this analysis. Blood pressure was measured at home twice daily according to international guidelines, and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0, and the European Society of Hypertension (ESH) criteria.**

Results. **Home-based measurements detected significantly more cases of hypertension than in-clinic measurements did, according to the ESH criteria (54.6% versus 24.4%; $p < .001$) or the NCI-CTC (42.9% versus 22.7%; $p = .0015$). Very early hypertension (within 42 days, according to the ESH criteria) but not hypertension (occurring at any time during treatment period) was predictive of response ($p = .0011$ and $p = .26$, respectively).**

Conclusions. **Our preliminary results indicate that home-based measurement and grading according to the ESH criteria represents a reliable method to detect bevacizumab-induced hypertension. Whether hypertension is a biomarker of bevacizumab activity remains to be determined in a prospective study.** *The Oncologist* 2011;16:1325–1332

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Background

Hypertension is a common toxicity of anti-vascular endothelial growth factor (VEGF) agents, including bevacizumab (Avastin®; Genentech Inc, South San Francisco, CA) [1]. A recent meta-analysis of randomized controlled trials [2] indicated that patients receiving bevacizumab had a relative risk of 3.0 (95% confidence interval [CI], 2.2–4.2) for developing hypertension. Hypertension induced by anti-VEGF agents is usually easily managed by common medical treatment [1]. However, up to 16% of patients may develop severe hypertension requiring multidrug therapy [2]. Moreover, hypertension-related disorders such as stroke, myocardial infarction, and posterior reversible leukoencephalopathy have been reported, with a higher incidence in patients aged >65 years or with a past history of an arterial thromboembolic event (ATE) [3].

Beyond morbidity and mortality issues raised by bevacizumab-induced hypertension, it has been suggested that the occurrence of hypertension during anti-VEGF therapy could predict response [4]. However, a number of methodological biases may compromise the use of hypertension as a surrogate marker for the activity of anti-VEGF agents.

Firstly, hypertension is usually graded according to the National Cancer Institute Common Toxicity Criteria NCI-CTC [5], a classification mostly based on therapeutic interventions rather than blood pressure (BP) levels, which may underestimate the incidence of hypertension [1, 4]. Secondly, assessment of BP in clinical trials is performed at each cycle (i.e., every 2 or 3 weeks). One could expect that a closer assessment of BP may provide evidence of higher rates of hypertension, as recently highlighted in patients receiving sunitinib [6, 7]. Finally, a number of trials on anti-VEGF agents describe patients with metastatic renal cancer (mRCC) who previously underwent nephrectomy. Patients with only one kidney may be at higher risk for developing hypertension, and should be analyzed separately in further studies focusing on hypertension associated with anti-VEGF agents [1, 4, 6].

Hence, given the lack of standardized follow-up of BP in the medical oncology community and the above-mentioned methodological biases, the true incidence of bevacizumab-induced hypertension and its potential relationship with outcomes remain unclear. These specific issues are addressed in the present study of BP changes during bevacizumab therapy, which determined a reliable method for the detection and grading of hypertension and established recommendations for further studies aiming to study hypertension as a biomarker for bevacizumab efficacy.

Patients and Methods

A prospective, observational study was conducted in a cohort of adult patients with various malignancies referred to the Teaching Hospital Cochin academic medical oncology unit located in Paris, France.

Patients were considered eligible for this study if they had advanced or metastatic cancer requiring bevacizumab-based chemotherapy. Because a dose–response effect has been described regarding the development of hypertension [2, 8], only patients receiving the same dose intensity of bevacizumab (2.5 mg/kg per week) were included. Exclusion criteria included: mRCC or prior nephrectomy, non-small cell lung cancer (NSCLC) with predominant squamous cell histology, active bleeding, grade ≥1 proteinuria or uncontrolled hypertension at the time of diagnosis, a recent (<6 months) ATE, and uncontrolled brain metastasis.

Colorectal cancer patients received 5-fluorouracil–based combination chemotherapy, whereas NSCLC and ovarian cancer patients received platinum-based combination chemotherapy, with bevacizumab at 5 mg/kg every 2 weeks or bevacizumab at 7.5 mg/kg every 3 weeks for an identical bevacizumab dose intensity of 2.5 mg/kg per week. Because forced hydration is mandatory to avoid cisplatin-induced nephrotoxicity, but also favors hypertension as a result of increased volemia, patients receiving cisplatin-based regimens were excluded. When patients had achieved a partial response and could not tolerate chemotherapy, bevacizumab was administered as a single agent until progression or intolerable toxicity.

Baseline BP was assessed twice in the in-clinic setting and was considered grade 0 for values <140/90 mmHg, according to the European Society of Hypertension (ESH) guidelines [9]. After giving informed consent, patients were provided with a BP automeasurement device approved by the French Health Products Safety Agency, typically an Omron™ M5-I (HEM-757-E) or Omron™ R5-I (HEM-630-E) (Omron Healthcare Europe, Amsterdam, The Netherlands) and received instructions to monitor their BP twice daily after a period of rest, in the supine position. Data were manually collected at each visit, and reported in a clinical trial database. In the in-clinic setting, BP was monitored twice at each visit or treatment administration, after a period of rest, in the supine position. Toxicity was assessed according to the NCI-CTC, version 3.0, and the ESH classifications [5, 9]. All patients were considered evaluable for toxicity, and response rates were reported on an intent-to-treat basis. Hypertension was defined by at least three grade ≥1 measurements (ESH or NCI-CTC) during two consecutive days. According to the ESH recommendations [9], patients received antihypertensive medication whenever indicated.

The primary objective of this study was to determine the incidence of hypertension as defined by the NCI-CTC and ESH criteria, measured daily at home or in the clinic. On the assumption that daily BP monitoring would detect grade

Table 1. BP level (mmHg) differences between the ESH criteria and the NCI-CTC v3.0

	ESH criteria (with different types of measurements)			
Category	**Office or clinic**	**24-hr (ambulatory)**	**Home (self)**	**NCI-CTC v3.0**
Optimal	SBP <120 and DBP< 80			–
Normal	SBP 120–129 and/or DBP 80–84			–
High normal	SBP 130–139 and/or DBP 85–89			–
Hypertension	SBP ≥140 and/or DBP ≥90	SBP ≥125 and/or DBP ≥80	SBP ≥135 and/or DBP ≥85	
Grade 1	SBP 140–159 and/or DBP 90–99			Asymptomatic, transient increase (<24 hrs) by >20 (DBP) or BP >150/100 if previously WLN
Grade 2	SBP 160–179 and/or DBP 100–109			Recurrent or persistent increase (≥24 hrs) by >20 (DBP) or BP >150/100 if previously WLN, monotherapy may be indicated
Grade 3	SBP ≥189 and/or DBP ≥110			Requiring two or more drugs, or more intensive therapy than previously
Grade 4	–			Life-threatening consequences (e.g., hypertensive crisis)
Grade 5	–			Death

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; ESH, European Society of Hypertension; NCI-CTC v3.0, National Cancer Institute Common Toxicity Criteria, version 3.0; SBP, systolic blood pressure; WLN, within the limits of normal.

3–4 hypertension in 20% of patients, a total of 107 patients was required to obtain a 99% CI of ±10%. Secondary objectives included description of the toxicity profile and factors associated with the development of hypertension.

In view of recent publications correlating the occurrence of hypertension and response to anti-VEGF agents [4], the potential relationship between various thresholds of BP elevation (Table 1) and clinical outcomes was also assessed in this cohort of patients. We examined whether response could be predicted by (a) hypertension occurring at any time during bevacizumab therapy, (b) hypertension occurring within 56 days after initiation of bevacizumab, and (c) hypertension occurring within 42 days after initiation of bevacizumab. These temporal cutoffs were chosen after the initiation of the study, because a 56-day cutoff was examined in other studies and the 42-day cutoff corresponds to the lowest denominator for different schedules of administration of bevacizumab (i.e., the initiation of the fourth cycle for patients receiving bevacizumab every 2 weeks and the initiation of the third cycle for patients receiving bevacizumab every 3 weeks), making this cutoff easy to use for in-clinic monitoring.

Tumor evaluation was performed every four cycles of treatment, or before if clinically indicated, according to World Health Organization criteria [10]. The effect of several baseline pretreatment variables on activity and toxicity was evaluated, including cardiovascular risk factors, comedications, medical history, primary tumor, baseline hemoglobin, lymphocyte count, C-reactive protein, serum creatinine, and albumin.

Descriptive statistics were used to analyze patient characteristics (mean, median, 99% CI). Univariate analysis was carried out to correlate baseline characteristics with efficacy and toxicity criteria. To take into account the small population size in subgroup analyses, a p-value $< .01$ was considered statistically significant, and, therefore, 99% CIs of the proportions and hazard ratios were computed. Calculations were performed with NCSS™ 2007 software (NCSS, Kaysville, UT).

Results

From May 2005 to January 2009, a total of 184 patients received bevacizumab in our institution. Sixteen patients who had nephrectomy, 15 patients who did not meet other inclusion criteria, and 10 patients who were treated in other clinical trials were excluded from this study. Of the remaining 143 patients, 24 (16.8%) did not follow the above-mentioned instructions regarding BP monitoring (>10% of scheduled home measurements missing) and were excluded as well. The final cohort included 119 patients, including 63 males, with a median age of 62 years (range, 38–86 years).

Table 2. Patient baseline characteristics

Primary tumor type	Colorectal cancer	NSCLC	Ovarian cancer	Total
n (%)	46 (38.7)	48 (40.3)	25 (21.0)	119 (100)
Age, yrs: median (range)	61 (40–82)	61.5 (38–86)	62 (40–78)	62 (38–86)
Gender: male/female, *n* (%)	28 (60.9)/18 (39.1)	35 (72.9)/13 (27.1)	0 (0)/25 (100)	63 (52.9)/56 (47.1)
n of metastatic sites: *n* (%)				
1	20 (43.5)	26 (54.2)	12 (48)	58 (48.7)
2	17 (37.0)	13 (27.1)	10 (40)	40 (33.6)
≥3	9 (19.5)	9 (18.7)	3 (12)	21 (17.7)
Cumulative dose of bevacizumab (mg/kg) received: median (range)	45 (15–195)	37.5 (10–160)	30 (15–30)	40 (10–195)
Performance status: *n* (%)				
0	7 (15.2)	6 (12.5)	5 (20)	18 (15.1)
1	33 (71.7)	25 (52.1)	15 (60)	73 (61.3)
2	6 (13.1)	16 (33.3)	5 (20)	27 (22.7)
3	0 (0)	1 (2.1)	0	1 (0.9)
CV risk factors: *n* (%)				
Smoking	11 (23.9)	32 (66.7)	6 (24)	49 (41.2)
Hypertension	15 (32.6)	10 (20.8)	4 (16)	29 (24.4)
Diabetes	4 (8.7)	3 (6.3)	0 (0)	7 (5.9)
Dyslipidemia	9 (19.6)	6 (12.5)	3 (12)	18 (15.1)
BMI >25 kg/m^2	5 (10.9)	1 (2.0)	2 (8)	8 (6.7)
History of cardiopathy or stroke	7 (15.2)	8 (16.7)	3 (12)	18 (15.1)
History of DVT or PE	3 (6.5)	6 (12.5)	2 (8)	11 (9.2)
Hemoglobin, g/dL: median (range)	12.5 (8.8–16.1)	12.4 (8.7–15.2)	12.3 (9.4–13.8)	12.4 (8.7–16.1)
Lymphocyte count, $\times 10^3$/L: median (range)	1,398 (530–4,000)	1,205 (200–4,000)	1,575 (349–4,700)	1,424 (200–4,700)
CRP, mg/L	6 (1.1–180)	8.9 (0.5–195)	4 (0.1–134)	7 (0.1–195)
Albumin, g/L	38.7 (26.5–53)	37 (25–45)	40 (28–49)	39 (25–53)

Abbreviations: BMI, body mass index; CRP, C reactive protein; CV, cardiovascular; DVT, deep venous thrombosis; NSCLC, non-small cell lung cancer; PE, pulmonary embolism.

Twenty-nine patients (24.4%) had a history of hypertension. Other baseline characteristics are described in Table 2. In total, 1,229 cycles of bevacizumab were administered (median, eight per patient; range, 2–39).

Bevacizumab-Induced Hypertension

Home BP Assessment Detects Higher Rates of Hypertension

Using home monitoring data, 51 patients (42.9%; 99% CI, 31.2%–54.6%) developed hypertension (all grades) according to the NCI-CTC, version 3.0, compared with 65 patients (54.6%; 99% CI, 42.9%–66.4%) according to the ESH criteria. The difference between the two classifications was not significant ($p = .09$). Using the in-clinic data only (as usually performed in previously published studies), we found hypertension rates of 22.7% (99% CI, 12.8%–32.6%) and 24.4% (99% CI, 14.2%–34.5%), according to the NCI-CTC and ESH criteria, respectively. According to both classifications, the difference with proportions observed using home data was statistically significant ($p = .0015$ and $p = 3.10^{-6}$, respectively). However, the difference between home and in-clinic measurements was not significant when considering only grade ≥2 hypertension ($p = .049$) or grade 3–4 hypertension ($p = .03$). In contrast, grade 1 hypertension was more efficiently detected by home-based measurements and ESH grading ($p = .008$). In all but two cases, ESH grade 1 hypertension was followed by grade 2 hypertension within 2 weeks.

Home BP Assessment Detects Higher Rates of Early Hypertension (According to the ESH Criteria)

Early (≤56 days of treatment) hypertension occurred in 21.9% (99% CI, 12.1%–31.6%, home BP data) and 11.8% (99% CI,

Table 3. Clinical and biological factors associated with the occurrence of grade ≥1 hypertension (ESH criteria)

Characteristic	Total		Patients with bevacizumab-induced hypertension		Patients without bevacizumab-induced hypertension		*p*-value
	n	%	*n*	%	*n*	%	
n of patients	119	100	65	54.6	54	45.4	
Age, yrs: median (range)	62 (38–86)		62 (38–78)		62 (40–86)		.22
Gender: male/female	63/56	53/47	38/27	58.5/41.5	25/29	46.3/53.7	.20
Primary tumor type:							
Colorectal cancer	46	38.7	26	40	20	37.0	.85
NSCLC	48	40.3	23	35.4	25	46.3	
Ovarian cancer	25	21.0	16	26.4	9	16.7	
n of metastatic sites:							
1–2	98	82.4	56	86.1	42	77.8	.33
≥3	21	17.6	9	13.9	12	22.2	
Cumulative dose of bevacizumab (mg/kg) received: median (range)	40 (10–195)		50 (15–195)		30 (10–20)		.0001
Performance status							
0–1	27	22.7	51	78.5	40	74.0	.67
2–3	73	77.3	14	21.5	14	26.0	
CV risk factors							
Smoking	49	41.2	28	43.0	21	38.9	.71
Hypertension	29	24.4	17	26.2	12	22.2	.67
Diabetes	7	5.9	5	7.7	2	3.7	.45
Dyslipidemia	18	15.1	9	13.8	9	16.7	.80
BMI >25 kg/m^2	8	6.7	4	6.2	4	7.4	1.00
History of cardiopathy or stroke	18	15.1	9	13.8	9	16.7	.80
History of DVT or PE	11	9.2	5	7.7	6	4.1	.54
Hemoglobin, g/dL: median (range)	12.4 (8.7–16.1)		12.3 (8.7–15.2)		12.5 (8.8–16.1)		.47
Lymphocyte count, $\times 10^3$/L: median (range)	1,424 (200–4,700)		1,390 (200–4,700)		1,440 (200–4,000)		.34
CRP, mg/L: median (range)	7 (0.1–195)		6 (0.1–141)		6.5 (0.9–195)		.32
Albumin, g/L: median (range)	39 (25–53)		38.4 (27–49)		37 (25–53)		.61

Abbreviations: BMI, body mass index; CRP, C reactive protein; CV, cardiovascular; DVT, deep venous thrombosis; ESH, European Society of Hypertension; NSCLC, non-small cell lung cancer; PE, pulmonary embolism.

4.2%–19.4%, in-clinic BP data) of patients ($p < .001$). Very early (≤ 42 days of treatment) hypertension occurred in 17.7% (99% CI, 8.7%–26.7%, home BP data) and 6.6% (99% CI, 1.9%–15.0%, in-clinic BP data) of patients ($p < .001$).

Factors Predicting the Occurrence of Hypertension (According to the ESH Criteria, Occurring at Any Time During Treatment)

By univariate analysis, the only baseline parameter associated with the development of hypertension was the cumulative dose of bevacizumab ($p = .0001$). Other clinical and biological baseline characteristics were not associated with the development of hypertension (Table 3).

Retrospective Assessment of Activity and BP Levels

No correlation was found between the response rate and the development of hypertension (at home or in the clinic, graded using the NCI-CTC or ESH criteria). However, patients who developed very early hypertension (≤42 days,

Table 4. Antitumor activity according to blood pressure

Best response at first evaluation	Patients with BIH	Patients without BIH	*p*-value	Patients with very early BIH	Patients without very early BIH	*p*-value	Total
CR + PR	29	18	.26	16	31	.0011	47
SD	21	25		2	44		46
PD	15	11		3	23		26

Abbreviations: BIH, bevacizumab-induced hypertension; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

grade ≥1 according to the ESH criteria, measured at home or in the clinic) had significantly higher response rates than patients who did not experience this early toxicity (p = .0011) (Table 4). This statistically significant difference was observed in the three tumor groups (colorectal cancer, NSCLC, and ovarian cancer).

Finally, the incidence of hypertension (occurring at any time during the treatment period) was examined in the 39 patients who received >12 cycles of bevacizumab. Twenty-eight patients (71.8%; 99% CI, 53.2%–90.4%) developed grade ≥1 hypertension during the treatment period, suggesting that prolonged exposure to bevacizumab might increase the risk for developing hypertension.

Discussion

Hypertension is a frequent side effect of anti-VEGF therapy. However, various methods of grading and frequency of assessment of BP have been described in previous studies, suggesting potentially misleading conclusions regarding the incidence of hypertension or its potential role as a surrogate marker of efficacy for anti-VEGF agents [4].

This single-center, observational prospective study was designed to compare various methods of BP measurement and grading in patients receiving bevacizumab-based chemotherapy. The study found that grading according to the ESH criteria instead of the NCI-CTC could not detect significantly more cases of hypertension according to in-clinic measurements. However, home-based, twice-daily self-measurement of BP identified more patients developing hypertension than in-clinic measurements did. This difference was significant for all-grade hypertension, but did not translate for grade ≥2 hypertension, suggesting that home-based BP monitoring is useful to detect grade 1 (ESH) hypertension. Importantly, grade 1 hypertension was frequently followed by higher BP elevations, suggesting that detecting grade 1 hypertension could allow identification of patients requiring further antihypertensive therapy.

Early (≤56 days of treatment) and very early (≤42 days of treatment) hypertension were more accurately described using home-based, twice-daily BP measurement, a result that was expected given the rarity of high-grade hypertension during the first weeks of treatment [11].

Taken together, these findings from the prospective part of the study suggest that home-based daily BP assessment was the more reliable method to detect bevacizumab-induced hypertension, whereas grading according to the ESH criteria was more sensitive in detecting early BP elevation.

Furthermore, a high proportion of patients (71.8%) who received ≥12 cycles of bevacizumab developed hypertension, a finding consistent with the knowledge that the risk for developing bevacizumab-associated hypertension appears constant over time [11, 12]. The cumulative dose received was strongly correlated with the occurrence of hypertension, whereas a past history of hypertension was not. This lack of association could be explained by the use of antihypertensive agents in these patients.

Furthermore, the potential correlation between antitumor activity and the development of hypertension during bevacizumab therapy was examined. In contrast with previous reports [13], no correlation between the development of hypertension occurring at any time during bevacizumab therapy and the response rate was seen. This could be explained by the small size of the study population, which was not determined for this specific analysis. However, this finding may appear contradictory to the above-mentioned knowledge that the risk for developing bevacizumab-associated hypertension appears constant over time. Hence, two categories of patients may develop hypertension during bevacizumab therapy: (a) patients receiving long-lasting bevacizumab therapy (i.e., patients with a response to bevacizumab therapy), who may develop late-onset hypertension, and (b) patients with early hypertension. In this latter group, higher response rates were observed (as detailed above), suggesting that the two groups may overlap and accounting for the lack of association between activity and hypertension when considering hypertension occurring at any time during the treatment period.

This analysis indicated statistically higher response rates in patients who developed very early (≤42 days of

treatment) hypertension (grade ≥1 according to the ESH criteria). This finding was previously described by Scartozzi et al. [14] and Friberg et al. [15] in colorectal and pancreatic cancer patients receiving bevacizumab-based chemotherapy, although these observations examined hypertension occurring within 56 days of treatment.

Another illustration of the accuracy of this finding was provided by Rixe et al. [16–18], who used a threshold of diastolic BP ≥90 mmHg to describe a relationship between clinical activity and hypertension induced by sunitinib or axitinib in phase II studies. This threshold overlaps with the ESH definition of grade 1, in-clinic hypertension (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) and appears easy to use in daily practice.

One may hypothesize that higher BP values could reflect a higher exposure to anti-VEGF drugs, and therefore establish a pharmacokinetic/pharmacodynamic relationship accounting for this relationship. In a recent analysis in mRCC patients receiving axitinib, Rixe et al. [19] found significantly better outcomes in patients who experienced at least one in-clinic measurement of diastolic BP ≥90 mmHg, as well as in patients with an axitinib area under the curve (AUC) above the median. However, there was no apparent correlation between AUC and maximum diastolic BP during axitinib therapy in that study, suggesting a more complex mechanism explaining the potential relationship between response and hypertension during anti-VEGF therapy. Most recently, a correlation between sorafenib-induced BP elevation on the first day of treatment and its efficacy in 54 cancer patients was evidenced [20]. No correlation was found between variability in BP and steady-state sorafenib plasma concentrations. Hence, further studies including pharmacokinetic data and mechanistic analyses of BP elevation (possibly including arterial stiffness assessments) are required to better characterize this phenomenon.

Whether hypertension could represent a biomarker for the activity of anti-VEGF agents remains to be determined, by the means of a prospective study addressing this specific issue. Hence, it has been proposed that dose escalation of the drug until BP elevation in an individual patient might lead to better activity [21]. Conversely, the lack of hypertension during anti-VEGF therapy might justify an early change in therapy. The present analysis provides a potential threshold for early evaluation of bevacizumab-induced hypertension: grade ≥1 hypertension (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) occurring within 42 days of treatment.

Conclusions

This prospective, observational study established that home-based daily BP measurement is an accurate and reliable method to detect bevacizumab-induced hypertension. The analysis of activity data suggests a relationship between very early hypertension and the activity of bevacizumab-based regimens. Our preliminary results deserve confirmation in future prospective studies including bevacizumab dose escalation based on BP assessment.

Author Contributions

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"Hollyhocks for Hope" by Gail, a cancer patient, Botswana